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Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database

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Abstract: **INTRODUCTION:** Thymic carcinoma is a rare and aggressive thymic neoplasm. The European Society of Thoracic Surgeons developed a retrospective database collecting patients undergoing resection for thymic tumors from 1990 to 2010. **METHODS:** Of 2265 patients with thymic tumors, there were 229 thymic carcinomas. Clinicopathological characteristics were analyzed including age, associated paraneoplastic diseases, stage (Masaoka-Koga), World Health Organization histologic subtypes, type of resection (total/subtotal/biopsy/no resection), tumor size, pre/postoperative treatments, and recurrence. Outcome measures included overall survival (OS), freedom from recurrence, and cumulative incidence of recurrence. **RESULTS:** A complete resection was achieved in 140 patients (69%). Recurrence occurred in 54 patients (28%). Five- and 10-year OS rates were 0.61 and 0.37. Five- and 10-year freedom from recurrence rates were 0.60 and 0.43. Cumulative incidence of recurrence was 0.21 (3 yr), 0.27 (5 yr), and 0.32 (10 yr). Survival was better after surgical resection versus biopsy/no resection ($p < 0.001$), after complete resection versus subtotal resection ($p < 0.001$), and when using Masaoka-Koga system (stages I-II versus III versus IV) ($p < 0.001$). The use of multidisciplinary treatments resulted in a survival advantage which was significant in the surgery + radiotherapy group ($p = 0.02$). Incomplete resection ($p < 0.0001$) and advanced stage (Masaoka-Koga III-IV) ($p = 0.02$) had a negative impact on OS at multivariable analysis. Administration of adjuvant radiotherapy was beneficial in increasing OS ($p = 0.02$). **CONCLUSIONS:** The results of our study indicate that patients with thymic carcinoma should undertake surgical resection whenever possible; a complete resection and early Masaoka-Koga stage are independent predictors of improved survival; our results also suggest that postoperative radiotherapy is beneficial in improving survival.

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Thymic Carcinoma: A Cohort Study of Patients from the European Society of Thoracic Surgeons Database

Enrico Ruffini, MD,* Frank Detterbeck, MD,† Dirk Van Raemdonck, MD,‡ Gaetano Rocco, MD,§ Pascal Thomas, MD,|| Walter Weder, MD,¶ Alessandro Brunelli, MD,# Francesco Guerrera, MD,* Shaf Keshavjee, MD,** Nasser Altorki, MD,†† Jan Schützner, MD,‡‡ Alex Arame, MD,§§ Lorenzo Spaggiari, MD,||| Eric Lim, MD,¶¶ Alper Toker, MD,### Federico Venuta, MD***; and the European Society of Thoracic Surgeons Thymic Working Group†††

Introduction: Thymic carcinoma is a rare and aggressive thymic neoplasm. The European Society of Thoracic Surgeons developed a retrospective database collecting patients undergoing resection for thymic tumors from 1990 to 2010.

Methods: Of 2265 patients with thymic tumors, there were 229 thymic carcinomas. Clinicopathological characteristics were analyzed including age, associated paraneoplastic diseases, stage (Masaoka-Koga), World Health Organization histologic subtypes, type of resection (total/subtotal/biopsy/no resection), tumor size, pre/postoperative treatments, and recurrence. Outcome measures included overall survival (OS), freedom from recurrence, and cumulative incidence of recurrence.

Results: A complete resection was achieved in 140 patients (69%). Recurrence occurred in 54 patients (28%). Five- and 10-year OS

rates were 0.61 and 0.37. Five- and 10-year freedom from recurrence rates were 0.60 and 0.43. Cumulative incidence of recurrence was 0.21 (3 yr), 0.27 (5 yr), and 0.32 (10 yr). Survival was better after surgical resection versus biopsy/no resection ($p < 0.001$), after complete resection versus subtotal resection ($p < 0.001$), and when using Masaoka-Koga system (stages I–II versus III versus IV) ($p < 0.001$). The use of multidisciplinary treatments resulted in a survival advantage which was significant in the surgery + radiotherapy group ($p = 0.02$). Incomplete resection ($p < 0.0001$) and advanced stage (Masaoka-Koga III–IV) ($p = 0.02$) had a negative impact on OS at multivariable analysis. Administration of adjuvant radiotherapy was beneficial in increasing OS ($p = 0.02$).

Conclusions: The results of our study indicate that patients with thymic carcinoma should undertake surgical resection whenever possible; a complete resection and early Masaoka-Koga stage are independent predictors of improved survival; our results also suggest that postoperative radiotherapy is beneficial in improving survival.

Key Words: Thymic carcinoma, Staging, Prognostic factors, Thymic tumors, Surgery.

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*Section of Thoracic Surgery, Department of Surgery, University of Torino, Torino, Italy; †Section of Thoracic Surgery, Yale University, New Haven, Connecticut; ‡Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; §Department of Thoracic Surgery, National Cancer Institute, Pascale Foundation, Naples, Italy; ||Department of Thoracic Surgery, Aix-Marseille University, Marseille, France; ¶Department of Thoracic Surgery, University Hospital, Zurich, Switzerland; #Division of Thoracic Surgery, St. James's University Hospital, Leeds, United Kingdom; **Department of Thoracic Surgery, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; ††Department of Thoracic Surgery, New York Presbyterian Hospital-Weill Cornell Medical Center, New York, New York; ‡‡3rd Department of Surgery, First Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; §§Department of thoracic surgery, Hopital Europeen Georges-Pompidou and Hopital Laennec, Paris, France; |||Department of Thoracic Surgery, European Institute of Oncology, Milan, Italy; ¶¶Department of Thoracic Surgery, Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Division, Imperial College, London, United Kingdom; ###Department of Thoracic Surgery, Istanbul University, Istanbul Medical School, Istanbul, Turkey; ***Department of Thoracic Surgery, University of Rome SAPIENZA, Policlinico Umberto I, Fondazione Eleonora Lorillard Spencer Cenci, Rome, Italy. †††The list of authors included in the European Society of Thoracic Surgeons Thymic Working Group are provided in Appendix 1.

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Address for correspondence: Enrico Ruffini, MD, Thoracic Surgery, University of Torino, 3, Via Genova 10126, Torino, Italy. E-mail: enrico.ruffini@unito.it

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Thymic tumors are rare neoplasms, although they represent the most frequent anterior mediastinal tumors. According to the latest World Health Organization (WHO) histologic classification, thymic tumors are divided in thymomas and thymic carcinomas, the latter including the rare neuroendocrine thymic tumors (NETTs). The distinction between thymomas and thymic carcinomas reflects a different histologic and molecular pattern and a different clinical and prognostic behavior. Thymic carcinomas usually present with locally advanced stages, an aggressive behavior, and a frequent incidence of lymphatic or distant metastases. As a consequence, survival rates are lower than those observed in thymomas.^{1–3}

Due to the rarity of these tumors, only small series have been published so far on thymic carcinomas, with conflicting results about the prognostic factors and optimal management.

The last decade has witnessed a dramatic increase of the interest in thymic malignancies, culminated with the creation of several thymic interest groups, and the foundation of the

International Thymic Malignancies Interest Group (ITMIG) in 2010.

The European Society of Thoracic Surgeons (ESTS) thymic working group developed a retrospective database among interested centers to collect patients operated on for thymic tumors from 1990 to 2010. The aim of this study was to investigate the population of patients with thymic carcinomas submitted to surgical resection using the ESTS retrospective thymic database, to identify possible prognostic factors and to evaluate optimal therapeutic strategies.

MATERIALS AND METHODS

The ESTS enquired among its members about participation to the ESTS retrospective database thymoma project to collect patients with thymic malignancies submitted to surgery from 1990 to 2010. Follow-up data were collected until December 2011. Overall, 36 institutions replied, including 28 from Europe, five from United States/Canada, and three from Asia (Appendix 2). Institutional review board approval was obtained at each institution.

Of 2265 patients with thymic malignancies, 229 thymic carcinomas were identified. NETTs were excluded. Recording variables in the data set included demographics, the presence of associated paraneoplastic syndromes, histology, 2004 WHO classification,⁴ tumor size measured as the largest diameter on the surgical specimen, tumor staging according to Masaoka-Koga,⁵ completeness of resection, administration of preoperative (primary) or postoperative (adjuvant) treatment, type of surgical procedure, cause of death (when available), and recurrence. Clinical (preoperative) staging was assessed in all cases by computed tomography scan, integrated by magnetic resonance imaging to assess great vessel invasion in selected patients. Integrated positron emission tomography (PET)-computed tomography (CT) was used by most centers to exclude distant metastases. No center employed tumor, node, metastasis (TNM)-based staging systems. We had no sufficient information about the nodal status and the site of distant metastases to draw any conclusion about their role as prognostic factors. Patients operated on before 2004 were reclassified at each center using the latest WHO histologic classification. Histologic specimens were assessed in each center by pathologists experienced in thymic malignancies, and the differential diagnosis between thymic carcinoma/thymoma/lung cancer was performed in each center based on morphological evaluation and using immunohistochemistry (CD5 and KIT staining) when indicated.

Study outcomes included overall survival (OS), freedom from recurrence (FFR), and the cumulative incidence of recurrence (CIR). OS was computed from the date of surgery to the date of death (any cause). FFR was computed from the date of surgery to the date of recurrence or death (any cause). CIR was calculated from the date of surgery to the date of recurrence. Death from any cause was considered as a competing event in FFR analysis.⁶ Patients alive or without recurrence were censored on the date of the last follow-up. OS was calculated on the entire population, whereas FFR and CIR were evaluated in patients receiving a complete (R0) resection and complete information on recurrence status.

Statistical Analysis

The Kaplan–Meier product-limit method was used to compute OS and FFR. The log-rank test was used to assess the differences between survival rates. The Nelson–Aalen method was used to calculate the CIR. Univariable and multivariable Cox proportional hazard models with shared frailty were employed to evaluate OS prognostic factors. Evaluated predictors included age at surgery (as continuous), sex, Masaoka-Koga stage (I–II versus III–IV), tumor size (as continuous), histology (squamous cell versus other subtypes), resection status (complete/incomplete), associated Myasthenia Gravis (MG), and administration of primary (preoperative) and adjuvant (postoperative) treatment. FFR analysis was undertaken using competing-risks regression models (Fine and Gray method), taking into account death by any causes as competing event. The missing data in the different analyses were multiple imputed; 10 imputed data sets provided the combined estimates. Chi-square test and Fisher's exact test, when appropriate, were used to evaluate the differences between groups. The statistical analysis was performed using STATA (version 12.1; StataCorp LP, College Station, TX).

RESULTS

The median contribution by institution was four patients (range, 1–28); 23 institutions (68%) provided less than five patients, seven institutions (21%) provided six to 15 patients, and four institutions (11%) contributed with more than 15 patients.

Median follow-up time was 44 months (interquartile range [IQR], 67 mo; range, 2–214).

Follow-up data were complete in 73% of the patients at the end of the follow-up period (December 31, 2011).

Figure 1 illustrates the flow of patients according to the different end points. Two hundred fifteen patients were available for OS analysis; FFR and recurrence analysis could be performed on 113 patients.

Clinical Data

The characteristics of the cohort population ($n = 229$) are illustrated in Table 1. Median age at surgery was 58 years, ranging from 22 to 88 years, and 58% of the patients (133 of 229) were men. Associated MG was observed in 31 of 229 patients (14%). The most frequent histologic subtypes were squamous cell carcinoma (98 of 129 patients, 76%), followed by mucoepidermoid type (10 patients, 8%). Median tumor size at surgery (largest diameter) was 5 cm (range, 1–25 cm). According to resection status, a complete (macro and microscopic) resection (R0) was achieved in 140 of 203 patients (69%); an incomplete resection was performed in 47 patients, of whom there were 23 microscopic (R1) and 24 macroscopic (R2) residuals; 16 patients received only biopsy (no resection). According to Masaoka-Koga stage, the majority of patients were at advanced stages (stages III–IV, 132 of 186, 71%). One-third of the patients (78 of 215) received preoperative (primary) therapy, mostly chemotherapy, including four patients stage I, three patients stage IIa, six patients stage IIb, 31 patients stage III, 15 patients stage IVa, and five patients stage IVb (14 patients with missing information). Indications

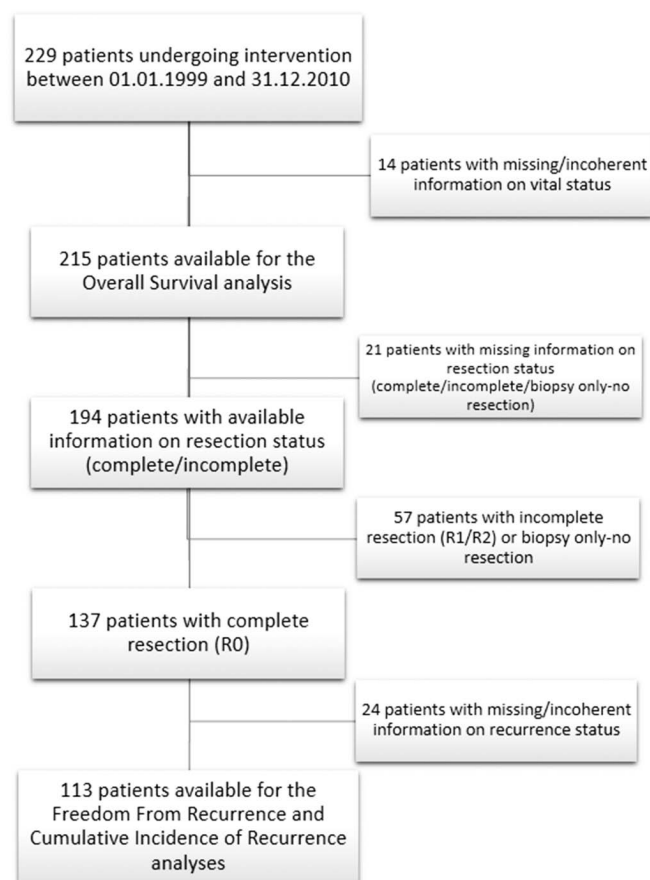


FIGURE 1. Study flow diagram of the patient population.

to preoperative therapy depended on each center's experience, although it was more frequently employed in more advanced stages and when a complete resection could not be anticipated at preoperative clinical evaluation. Adjuvant therapy after surgery was employed in 69% of the patients (149 of 215), including 16 patients stage I, six patients stage IIa, 11 patients stage IIb, 58 patients stage III, 20 patients stage IVa, and nine patients stage IVb (29 patients with missing information). Indications to adjuvant therapy also depended on each center's experience, although there were no differences between early and advanced stages ($p = 0.27$) and between R0 and R+ patients ($p = 0.45$). The most frequent type of adjuvant therapy was radiation therapy, either alone ($n = 59$) or combined with chemotherapy ($n = 72$). Resectability rates were found to be lower in squamous cells carcinoma (78% versus 81%, $p = 0.06$), and they decreased with stage (I 91%; IIa 62%; IIb 74%; III 66%; IVa 28%; IVb 19%).

Survival Analysis

At the end of the study period, 92 patients died. Of these, 37 died from tumor-related causes. Fifty-four patients (28%) experienced a recurrence at follow-up. In 47 cases, location of recurrence was assessed, including 24 local/regional (12 pleura, eight mediastinum, two lymphnodes, and two locoregional not otherwise specified [NOS]) and 23 distant (12 lung, three liver, three bones, and five distant NOS) recurrences.

TABLE 1. Characteristics of the Patient Population

	<i>n</i>	%	Median
Sex (male)	133	58	
Age (continuous)			58
Myasthenia Gravis (yes)	31	14	
Recurrence	54	28	
Tumor size			5
Type of intervention and surgical approach ($n = 217$)			
Biopsy only/no resection	16	7	
Sternotomy	136	62	
Thoracotomy	25	12	
Extended approach ^a	25	12	
VATS/robotic	15	7	
Histology ($n = 129$)			
Squamous cell carcinoma	98	76	
Basaloid	4	3	
Clear cell	4	3	
Lymphoepithelioma like	5	4	
Mucoepidermoid	10	8	
Sarcomatoid	6	5	
Undifferentiated carcinoma	2	1	
Resection status ($n = 203$)			
R0	140	69	
R1	23	11	
R2	24	12	
Biopsy only	16	8	
Masaoka-Koga stage ($n = 186$)			
I	22	12	
IIa	13	7	
IIb	19	10	
III	80	43	
IVa	36	19	
IVb	16	9	
Preoperative (primary) therapy ($n = 215$)	78	36	
CT	53		
Radiotherapy	4		
CT + RT	21		
Postoperative (adjuvant) therapy ($n = 215$)	149	69	
CT	18		
RT	59		
CT + RT	72		

^aSternotomy + thoracotomy.

CT, chemotherapy; RT, radiotherapy; VATS, video-assisted thoracic surgery.

The 3-year, 5-year, and 10-year overall OS rates were 0.72 (95% confidence interval [CI], 0.65–0.78), 0.61 (95% CI, 0.54–0.68), and 0.37 (95% CI, 0.29–0.47). The 3-year, 5-year and 10-year overall FFR rates were 0.71 (95% CI, 0.61–0.79), 0.60 (95% CI, 0.49–0.69), and 0.43 (95% CI, 0.31–0.55). CIR was 0.21 (95% CI, 0.14–0.30) at 3 years, 0.27 (95% CI, 0.19–0.37) at 5 years, and 0.32 (95% CI, 0.23–0.45) at 10 years (Fig. 2A). It shows a steep increase in the first 5 years, followed by a slower increase up to 10 years and a trend to a plateau after 10 years.

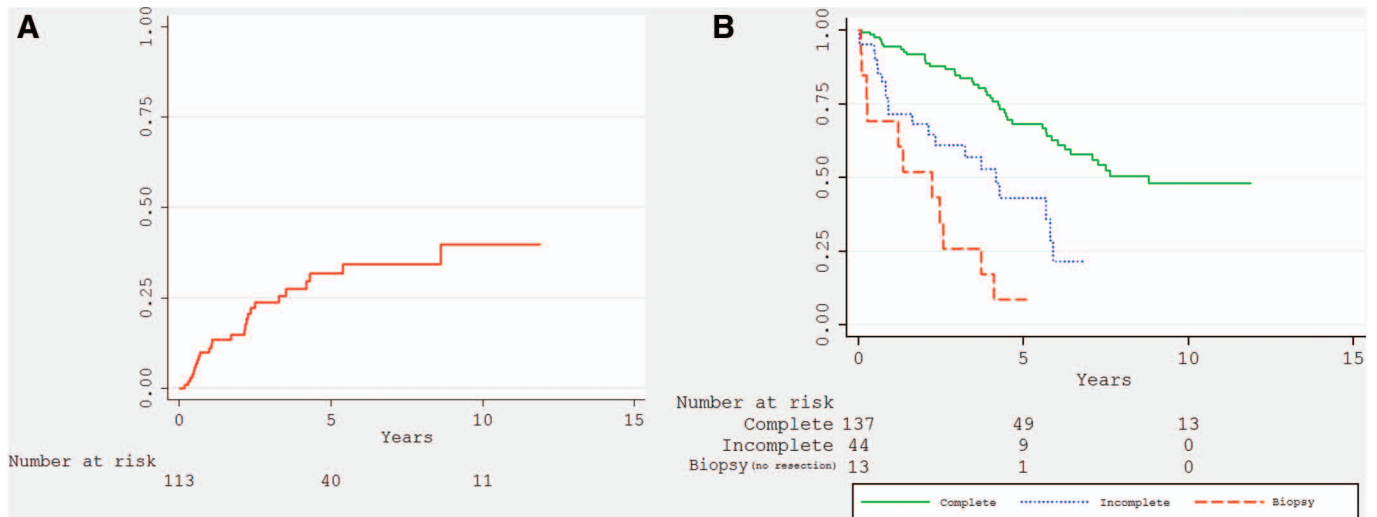


FIGURE 2. Cumulative incidence of recurrence (A) and survival by the type of intervention (B) in the patient population.

Survival rates by the type of surgery (biopsy/no resection only versus incomplete versus complete resection, Fig. 2B) suggest a significant survival advantage in case of surgical resection versus no resection (biopsy only/no resection) ($p < 0.001$). Complete resection was associated with a significant increased survival as compared with incomplete resection ($p < 0.001$), and incomplete resection resulted in a significant survival advantage versus biopsy only/no resection ($p = 0.01$).

Survival rates by Masaoka-Koga stage (stages I–II versus III versus IV) indicate a nice prognostic stratification across the stages (5-year OS: stages I–II, 0.79; stage III, 0.60; stage IV, 0.24; $p < 0.001$) (Fig. 3).

No survival difference was found according to histology (squamous cell versus others) (5-year OS: squamous, 0.72; others, 0.69; $p = 0.2$). We further compared survival rates of patients with thymic carcinoma with other types of thymic tumors in the ESTS database, including B3 thymomas and NETT. Five-year survival was similar in thymic carcinomas

versus NETT (0.61 versus 0.63, $p = 0.44$), although survival was significantly worse in thymic carcinomas versus B3 thymomas (0.61 versus 0.82, $p < 0.001$, Fig. 4).

We analyzed OS rates according to the type of treatment in the following patients groups (Table 2): surgery alone ($n = 32$), preoperative therapy + surgery ($n = 34$), surgery + adjuvant therapy (chemotherapy, radiotherapy, or combined chemoradiotherapy) ($n = 105$), and preoperative therapy + surgery + adjuvant therapy ($n = 42$). Using as a reference group the patients receiving surgery alone, the use of a multidisciplinary treatment resulted in a survival advantage which was found to be significant in the surgery + postoperative radiotherapy group (log-rank test, $p = 0.02$).

Prognostic Predictors

Table 3 shows the analysis of predictors using the two end points: OS and FFR.

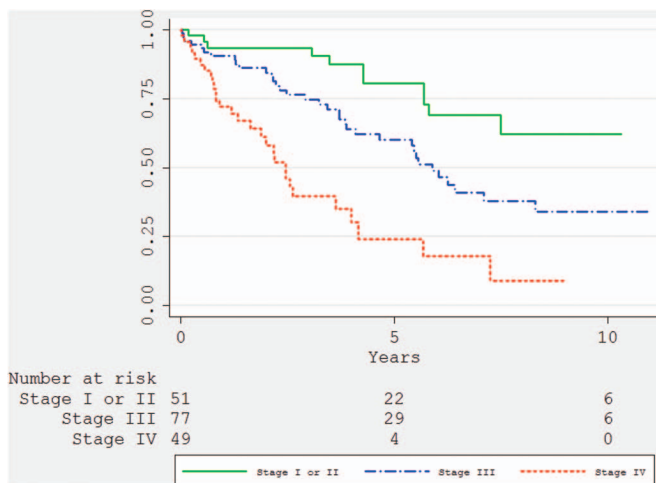


FIGURE 3. Survival curves by Masaoka-Koga staging system (stages I–II versus III versus IV).

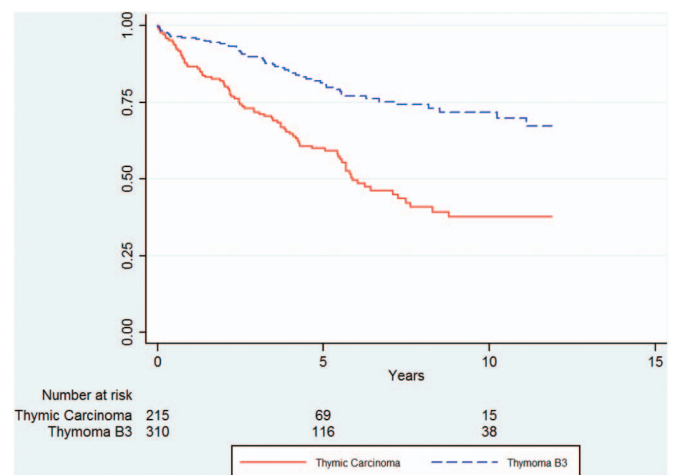


FIGURE 4. Survival curves of patients with thymic carcinoma ($n = 215$) and B3 thymomas ($n = 310$) in the ESTS thymic database. ESTS, European Society of Thoracic Surgeons.

TABLE 2. Survival and Log-Rank Test according to Treatments (Surgery Alone as Reference Group)

	<i>n</i>	<i>p</i>	3 yr (95% CI)	5 yr (95% CI)	10 yr (95% CI)
Surgery alone	32	(as reference)	0.65 (0.43–0.80)	0.61 (0.39–0.77)	0.28 (0.09–0.52)
Surgery + preoperative (primary) therapy	34	0.79	0.63 (0.43–0.77)	0.54 (0.34–0.70)	0.29 (0.10–0.52)
Surgery + postoperative (adjuvant) therapy	105	0.11	0.78 (0.66–0.84)	0.61 (0.50–0.71)	0.43 (0.29–0.56)
Surgery + CT adjuvant	14	0.94	0.65 (0.26–0.87)	0.50 (0.15–0.77)	0.17 (0.00–0.62)
Surgery + RT adjuvant	35	0.02	0.79 (0.59–0.90)	0.69 (0.47–0.83)	0.69 (0.47–0.83)
Surgery + CT and RT adjuvant	56	0.27	0.78 (0.63–0.87)	0.60 (0.44–0.72)	0.37 (0.21–0.53)
Surgery + preoperative and adjuvant therapy	42	0.28	0.75 (0.57–0.86)	0.70 (0.51–0.82)	0.38 (0.17–0.59)

CI, confidence interval; CT, chemotherapy; RT, radiotherapy.

TABLE 3. Univariate and Multivariate Analysis of Predictors for Overall Survival and Freedom from Recurrence

	Univariate Model					Multivariate Model				
	Hazard Ratio	SE	<i>p</i>	95% CI		Hazard Ratio	SE	<i>p</i>	95% CI	
				Lower	Upper				Lower	Upper
Overall survival—multiple imputation for missing data										
Sex (male)	1.03	0.22	0.883	0.67	1.58	0.99	0.23	0.975	0.63	1.55
Age (continuous, 1 yr)	1.03	0.01	0.001	1.01	1.05	1.03	0.01	0.006	1.01	1.04
Myasthenia Gravis (yes)	0.56	0.20	0.099	0.28	1.12	0.81	0.30	0.582	0.39	1.69
Tumor size (continuous, 1 cm)	1.01	0.04	0.709	0.94	1.10	0.99	0.05	0.773	0.89	1.09
Histology (squamous cell carcinoma vs. other)	1.11	0.34	0.73	0.60	2.04	1.25	0.46	0.54	0.60	2.61
Other										
Resection status (R0 vs. R1-2)	3.28	0.74	0.000	2.11	5.11	3.03	0.74	0.000	1.87	4.91
Masaoka-Koga stage (<i>n</i> = 186) I–II vs. III–IV	2.54	0.81	0.004	1.35	4.77	2.48	0.97	0.024	1.13	5.43
Preoperative (primary) therapy (yes)	1.10	0.25	0.683	0.70	1.71	0.84	0.22	0.510	0.49	1.42
Postoperative (adjuvant) therapy (yes)	0.64	0.15	0.053	0.41	1.01	0.55	0.15	0.025	0.33	0.93
Freedom from recurrence (end point: recurrence; competing: death)—multiple imputation for missing data										
Sex (male)	0.78	0.30	0.512	0.36	1.66	0.74	0.31	0.471	0.33	1.66
Age (continuous, 1 yr)	0.99	0.01	0.304	0.96	1.01	0.99	0.01	0.419	0.96	1.02
Myasthenia Gravis (yes)	0.22	0.21	0.118	0.03	1.46	0.31	0.33	0.265	0.04	2.46
Tumor size (continuous, 1 cm)	1.11	0.06	0.050	1.00	1.24	1.10	0.08	0.192	0.95	1.26
Histology (squamous cell carcinoma vs. others)	1.79	0.92	0.26	0.65	4.94	1.81	1.03	0.30	0.58	5.62
Others										
Masaoka-Koga stage (<i>n</i> = 186) I–II vs. III–IV	1.60	0.81	0.355	0.59	4.36	1.46	0.88	0.536	0.44	4.86
Preoperative (primary) therapy (yes)	1.84	0.76	0.140	0.82	4.12	1.28	0.63	0.609	0.49	3.34
Postoperative (adjuvant) therapy (yes)	0.63	0.24	0.234	0.29	1.35	0.78	0.36	0.594	0.32	1.94

CI, confidence interval.

Increased age ($p = 0.006$; hazard ratio [HR], 1.03; 95% CI, 1.01–1.04), incomplete resection ($p < 0.0001$; HR, 3.03; 95% CI, 1.87–4.91), and advanced stage (Masaoka III–IV) ($p = 0.02$; HR, 2.48; 95% CI, 1.13–5.43) had a negative impact on OS at multivariable analysis. Administration of adjuvant therapy (considered as a whole) was beneficial in increasing OS ($p = 0.02$; HR, 0.55; 95% CI, 0.33–0.92).

When analyzing FFR, no covariate proved to be significant at the multivariable analysis, while increased tumor size was a significant predictor of recurrence at univariable analysis ($p = 0.05$; HR, 1.11; 95% CI, 1.00–1.24).

DISCUSSION

The present study based on the ESTS retrospective thymic database represents to our knowledge the largest series of patients with thymic carcinoma submitted to surgical resection to date.

The results of our study indicate that (1) surgical resection improves survival over simple biopsy/no resection; (2) a complete resection is an independent predictor of survival; (3) the Masaoka-Koga staging system is an effective prognostic factor; and (4) the use of a multimodality approach including postoperative radiotherapy is effective in improving survival.

Thymic carcinomas are rare neoplasms, representing a 15% to 20% of all thymic tumors.^{7,8} Contrary to thymomas, they show cytologic atypia, lack of an organotypical appearance, and a resemblance to carcinomas occurring in most solid organs. Despite the term, thymic carcinomas represent a spectrum of tumors, which has been recently classified by WHO in 11 subtypes including the NETT.⁴

Clinically, thymic carcinomas most often present an aggressive behavior, are discovered at an advanced stage, and have a significantly lower survival than thymomas, with a 5-year survival of 30% to 60% in most series. Population-based studies indicate an average 16% resection rate in patients with thymic carcinoma,⁹ with a 5-year survival rate of 17% in non-resectable, advanced stages.¹⁰ Until recently, the rarity of these tumors has hampered a consensus about prognostic factors and optimal treatment strategies.

In the literature, many studies have considered thymic carcinomas and thymomas in the same analysis, sometimes grouping thymic carcinomas with advanced stages thymomas^{11,12} based on historical histologic classifications which defined thymic carcinomas as “type C” malignant thymomas^{3,13}; the denomination of B3 thymomas as “well-differentiated thymic carcinomas” further contributed to generate some confusion. The latest WHO histologic classification, however, clearly pointed out that thymic carcinomas are a distinct category of thymic tumors, which should be analyzed separately from thymomas. Although in the WHO classification, NETTs are included as a subgroup of thymic carcinoma and some studies included both categories in the analysis,^{14,15} their unique histologic and clinical characteristics, along with the association with peculiar endocrinopathies (MEN),¹⁶ suggest that they should be analyzed as a distinct category, and for this reason, they were excluded from the analysis in the present study.

All studies so far on thymic carcinomas have consistently demonstrated a significant survival advantage in surgically treated patients. Lee et al.¹⁷ on a population of 60 patients had a 5-year survival rates of 85%, 29%, and 17%, respectively, after complete, incomplete resection, and biopsy only. Kondo and Monden¹⁸ in a population of 154 patients with thymic carcinomas reported a 5-year survival of 67% following total resection, versus 30% after incomplete resection versus 24% when no surgical resection was performed. Weksler et al.¹⁹ on a large population based on the Surveillance, Epidemiology, and End Results (SEER) database found a 5-year survival of 58% in case of complete thymic excision versus 26% in patients who received no surgery. Our results corroborate those obtained on smaller series, with 5-year survival rates of 80%, 36%, and 19% following complete, incomplete resection, and biopsy only. Our analysis therefore strongly supports surgical resection whenever possible in these tumors. The role of incomplete resection in thymic carcinoma has been a matter of debate in the past. Some authors found that a subtotal resection carries a better prognosis than biopsy only,¹ whereas others^{17,18} failed to demonstrate any advantage of incomplete resection versus no resection at all. Our study indicates that an incomplete resection is significantly superior to no resection and therefore seems worth being carried out if a complete resection is not possible.

There is no general agreement about optimal staging system for thymic carcinomas. The Masaoka and Masaoka-Koga staging customarily applied in thymomas did not show a similar efficacy in thymic carcinomas by some authors.^{9,18,20–22} These authors found that significant survival differences were observed only when Masaoka stages were combined (stages I–II versus III–IV or stages I, II, III versus IV)²² or when other anatomical factors were taken into account (great vessels invasion).^{11,20} A TNM-based staging system has also been advocated for thymic carcinoma, based on the observation that up to 40% of thymic carcinomas present lymphnodal metastases which impact on long-term survival,²³ although the system failed to show significant survival differences in a Japanese study,²³ possibly due to the small number of patients. Weissferdt and Moran^{8,22} recently simplified the TNM system for thymic carcinomas into three-stage categories based on the extent of the regional involvement (stages I and II) and metastatic/distant disease (stage III) and found in their population ($n = 33$) a better prognostic stratification as compared with both Masaoka and standard TNM system. On the other hand, other series^{14,17,24} including a large series based on the SEER database¹⁹ indicate that advanced Masaoka stage is associated with a decreased survival. In our study, we found a good prognostic stratification among Masaoka stages (stages I and II were grouped because of a very similar survival). An ongoing joint International Association for the Study of Lung Cancer/ITMIG staging project collecting data from the most important thymic databases (ESTS, Japanese Association for Research on the Thymus [JART], ITMIG) is currently underway to come up with a proposal for a consistent staging system for thymic malignancies to be included in the forthcoming 8th edition of TNM system of thoracic malignancies. Although awaiting for these results, based on our results, we therefore suggest that Masaoka staging should be employed in thymic carcinomas.

Thymic carcinomas are customarily approached in a multimodality setting. A recent survey from the ESTS about optimal management of thymic tumors²⁵ indicates that 52% of the interviewed centers used a multimodality approach including radio and chemotherapy as adjunct to surgery in case of thymic carcinomas. Unfortunately, most of the studies evaluating the role of preoperative (primary) and postoperative (adjuvant) therapies following resection of thymic carcinomas showed conflicting and not uniform conclusions. Kondo and Monden¹⁸ found no survival differences in thymic carcinoma patients receiving surgery alone versus surgery plus adjuvant radiotherapy. Similar results are reported by Lee et al.¹⁷ on a smaller patient series. Other authors found a marginal beneficial effect of adjuvant radiotherapy.²⁶ Most studies evaluating the effect of adjuvant therapies included both thymoma and thymic carcinoma. In the present study, the use of a multimodality approach (either preoperative or postoperative or both) was found to be superior to surgery alone, with an OS advantage which proved to be significant in the surgery + adjuvant radiotherapy group. We are well aware that the different treatment groups were not randomly allocated and a selection bias cannot be excluded; nonetheless, our findings support the feeling that surgical resection might benefit from the use of a postoperative radiation treatment.

In the present study, tumor size and histology were not found to be significant prognostic factors on survival, although size was a predictor of recurrence at univariate analysis. In thymoma, tumor size was reported as a significant prognostic factor in some series,⁷ although size thresholds, exact measurements (largest diameter versus three-dimension measures), and the independent significance from Masaoka stage are all undefined issues which so far have not been elucidated yet. As for histology, the rarity of thymic carcinoma certainly represents a major limitation in the subgroup analysis by histologic subtypes, although some authors found a better survival for the squamous type as compared with the other carcinoma types.^{2,26} In the present study, when the squamous cell type ($n = 98$) was compared with all other subtypes ($n = 31$), no survival difference was observed, neither the squamous type showed an independent significance on survival or recurrence.

The presence of associated paraneoplastic syndromes is a distinct characteristic of thymic tumors. Although MG has been found to be present in approximately 30% to 35% of the patients with thymoma, the association of MG and thymic carcinoma is less often reported and still disputable. Although some authors maintain that MG cannot be associated with thymic carcinoma,^{9,27} a not negligible prevalence of MG in association with thymic carcinoma has been reported in the literature, ranging from 8%¹⁴ to 32%²⁸; the variable prevalence may possibly be the result of different patients referrals. Our 14% prevalence is in the range of that reported in the literature. Our survival analysis indicates that the presence of MG had no impact on either survival or recurrence.

The present study presents some strengths and limitations. The main strength is that it represents the largest series of patients with thymic carcinoma submitted to surgical resection to date. A major effort has been undertaken to achieve a homogeneous staging system and data information. Another strength was the exclusion of NETT from the analysis, which in our opinion represent a distinct group of high malignant thymic tumors and should therefore be considered separately. Among the limitations, unfortunately we did not have sufficient information about the nodal status of the resected thymic carcinomas and the site of distant metastases in stage IV patients to draw any conclusion about the impact of these covariates on survival. Another limitation includes the lack of a central pathology review; it is well known that a great interobserver variability has been reported for the WHO histologic classification of thymic malignancies,²⁹ particularly between B3 (well-differentiated thymic carcinoma) and thymic carcinoma. To reduce the possible merging of B3 cases into the thymic carcinoma population, we compared the survival curves of the patients with a diagnosis of B3 thymoma from the total ESTS database of thymic tumors with the patients with thymic carcinoma; the survival difference was significant (Fig. 4, $p < 0.001$), indicating that on average the histologic allocation was correct. Another limitation results from the collection of data from centers with a different geographic location, expertise, and volume activity, which might results in a heterogeneity of treatment strategies. Finally, the information about recurrence status, resection status, and perioperative treatments was not complete, with a loss of

statistical power particularly in the recurrence analysis and an anticipated underestimation of the CIR.

In conclusion, the results of the present retrospective study on a large population of patients with thymic carcinoma suggest that surgery is indicated whenever possible; a complete resection and an early Masaoka stage are predictors of improved survival. Our results also indicate that postoperative radiotherapy is beneficial in improving survival.

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APPENDIX 1. THE EUROPEAN SOCIETY OF THORACIC SURGEONS THYMIC WORKING GROUP

Khaled AlKattan: King Faisal Specialist Hospital, Alfaisal University, Riyadh, Saudi Arabia; Majed Refai: Ospedali Riuniti, Ancona, Italy; Caterina Casadio: University of Eastern Piedmont, Novara, Italy; Paolo Carbognani: University of Parma, Italy; Robert Cerfolio: University of Alabama at Birmingham, Birmingham, Alabama; Giovanni Donati: General Regional Hospital, Aosta, Italy; Christophoros N. Foroulis: Aristotle University of Thessaloniki, A.H.E.P.A. University Hospital, Thessaloniki, Greece; Cengiz Gebitekin: Uludag University School of Medicine, Bursa, Turkey; David Gomez de Antonio: Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; Kemp H. Kernstine: University of Texas, Southwestern Medical Center and School of Medicine, Texas; Bernhard Moser: Medical University of Vienna, Vienna, Austria; Cosimo Lequaglie: IRCCS-CROB Centro Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy; Moishe Liberman: Centre Hospitalier de l'Université de Montreal, University of Montreal, Montreal, Canada; Andrew G. Nicholson: Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Division, Imperial College, London, United Kingdom; Loic Lang-Lazdunski: Guy's Hospital, London, United Kingdom; Maurizio Mancuso: SS Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; Mario Nosotti: IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milano, Italy; Nuria M. Novoa: University Hospital of Salamanca, IBSAL, Salamanca, Spain; Geoffrey Brioude: Hôpital Nord-Aix-Marseille University, Marseille, France; Pier Luigi Filosso and Paolo Solidoro: University of Torino and AO Città della Salute e della Scienza di Torino, Italy; Salvatore Saita: Vittorio Emanuele Hospital, Catania, Italy; Marco Scarci: Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, United Kingdom; Alberto Terzi: Thoracic Surgery, Sacred Heart Hospital Negrar, Verona, Italy; Hans Van Veer: University Hospitals Leuven, Belgium; Marco Anile: University of Rome SAPIENZA, Policlinico Umberto I, Fondazione Eleonora Lorillard Spencer Cenci, Rome, Italy; Erino Rendina: University of Rome SAPIENZA, Ospedale S. Andrea, Fondazione Eleonora Lorillard Spencer Cenci, Rome, Italy; Luca Voltolini: University Hospital of Siena, Italy; and Wojciech Zurek: Medical University of Gdansk, Poland.

APPENDIX 2. LIST OF PARTICIPATING INSTITUTIONS

King Faisal Specialist Hospital Alfaisal University, Riyadh, Saudi Arabia; Hopital Europeen Georges-Pompidou and Hopital Laennec, Paris, France; Ospedali Riuniti, Ancona, Italy; University of Eastern Piedmont, Novara, Italy; University of Parma, Italy; University of Alabama at Birmingham, Birmingham, Alabama; General Regional Hospital, Aosta, Italy; Aristotle University of Thessaloniki, A.H.E.P.A. University Hospital, Thessaloniki, Greece; Uludag University School of Medicine, Bursa, Turkey; Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; University of Texas, Southwestern Medical Center and School of Medicine, Texas; Toronto General Hospital, University of Toronto, Canada; Medical University of Vienna, Vienna, Austria; IRCCS-CROB Centro Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy; Centre Hospitalier de l'Université de Montreal, University of Montreal, Montreal, Canada; Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Division, Imperial College, London, United Kingdom; Guy's Hospital, London, United Kingdom; SS Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; New York Presbyterian Hospital-Weill Cornell Medical Center, New York; IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milano, Italy; University Hospital of Salamanca, IBSAL, Salamanca, Spain; Hôpital Nord-Aix-Marseille University, Marseille, France; National Cancer Institute, Pascale Foundation, Naples, Italy; University of Torino, Torino, Italy; Vittorio Emanuele Hospital, Catania, Italy; Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, United Kingdom; 3rd Department of Surgery, First Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; S.Croce e Carle Hospital, Cuneo, Italy; Istanbul University, Istanbul Medical School, Istanbul, Turkey; University Hospitals Leuven, Belgium; University of Rome SAPIENZA, Policlinico Umberto I, Fondazione Eleonora Lorillard Spencer Cenci, Rome, Italy; University of Rome SAPIENZA, Ospedale S. Andrea, Fondazione Eleonora Lorillard Spencer Cenci, Rome, Italy; University Hospital of Siena, Italy; University Hospital, Zurich, Switzerland; Medical University of Gdansk, Poland; and European Institute of Oncology, Milan, Italy.

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